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**CHANGES IN SERUM LIPID CONCENTRATIONS
WITH AGE IN YOUNG MEN**

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FOREWORD

This report was prepared in the Biokinetics Branch by —

DALE A. CLARK, Ph.D.

The author gratefully acknowledges his indebtedness to Colonel L. J. Milch, Miss M. F. Allen, and members of the Cardiovascular Research Group, especially F. H. Wilson, for their contributions to this study, and to Dr. Bryan Danford for his helpful suggestions in preparing this report.

ABSTRACT

~~This report presents~~ data obtained during a longitudinal study of serum lipid levels in more than 400 men*. Between the ages of 19.6 and 27.5 years, these men exhibited significant increases in concentration of serum cholesterol, phospholipid, and low-density lipoproteins. Changes in cholesterol concentration are significantly associated with changes in S_{10-12} lipoprotein concentration. Changes in S_{20-400} lipoprotein and in body weight are less closely associated. Excess caloric intake and decreased exercise may have caused the lipid increases as the men advanced in age. The consistent decrease in serum high-density lipoprotein concentration may have resulted from processes of normal maturation, possibly changes in steroid hormone metabolism. Unequivocal evidence implicating steroid hormones is lacking.

* is presented.

This technical documentary report has been reviewed and is approved.

Robert B Payne

ROBERT B. PAYNE
Colonel, USAF, MSC
Chief, Operations Division

CHANGES IN SERUM LIPID CONCENTRATIONS WITH AGE IN YOUNG MEN

1. INTRODUCTION

A recent report from the Framingham study of cardiovascular disease calls attention to the occurrence of sudden death attributable to coronary heart disease in the male subjects of that study (1). The investigators report that, in 62.5% of sudden deaths caused by coronary heart disease, there was no clinical manifestation of the disease prior to the attack which caused death. This fact emphasizes the pertinence and urgency of research directed toward evaluating the degree to which atherosclerosis may involve the cardiovascular system in an individual who does not exhibit clinical symptoms attributable to the disease. The answer to this problem is not at hand, but pertinent data are being accumulated in the followup study on cardiovascular disease (2).

The subjects of this study are the men who entered the United States Military Academy at West Point in 1952. Of the total number of men in that original group, more than 400 have remained subjects in the study through 1960. Once every two years, each subject has provided a blood sample on which analyses have been performed for serum cholesterol, phospholipid phosphorus, and both high- and low-density lipoprotein concentrations; however, some analyses were not performed in the earlier years of this study. In 1960, a physical examination, certain x-rays, ECG tracings, and pertinent items of the subject's medical history were also obtained.

The aim of this study is to evaluate lipid levels as predictors of subsequent incidence of cardiovascular disease. The mean age of the

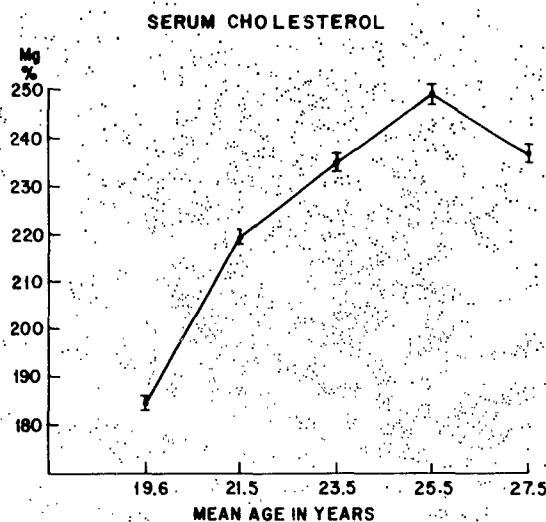


FIGURE 1

Mean concentration of serum cholesterol. Brackets enclose ± 1 standard error of the mean.

subjects was 27.5 years in 1960. It is therefore not surprising that there are no clinical symptoms of cardiovascular disease to be correlated with the lipid data. This report, therefore, will summarize changes that have occurred in the lipid and lipoprotein levels and point out some possible significance of the findings.

2. MATERIALS AND METHODS

The plan of the study, the analytic methods employed, and the findings through 1958, have been reported previously (2, 3, 4).

3. RESULTS AND DISCUSSION

In figure 1, the mean serum cholesterol concentration, in milligrams cholesterol per 100 ml.

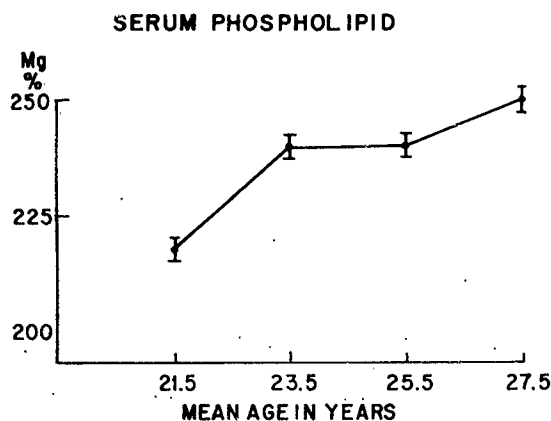


FIGURE 2

Mean concentration of serum phospholipid concentrations.

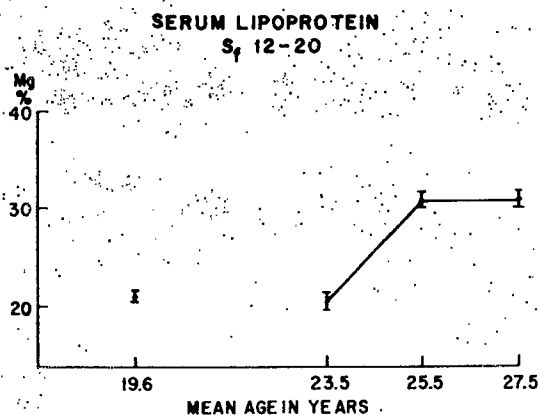


FIGURE 3

Mean concentration of serum lipoproteins, class S_f 12-20.

serum, is plotted against the mean age of the subject group. The mean cholesterol value is plotted as a point, and the brackets above and below each point enclose the range encompassed by ± 1 standard error of the mean. Each point in this figure, as well as in figures 2 to 9, represents the mean of more than 400 serum samples. From this graph it is apparent that the mean serum cholesterol concentration increased between the mean ages of 19.6 and 25.5 years and that it declined slightly but significantly during the last two-year sampling interval.

SERUM LIPOPROTEIN S_f 20-400

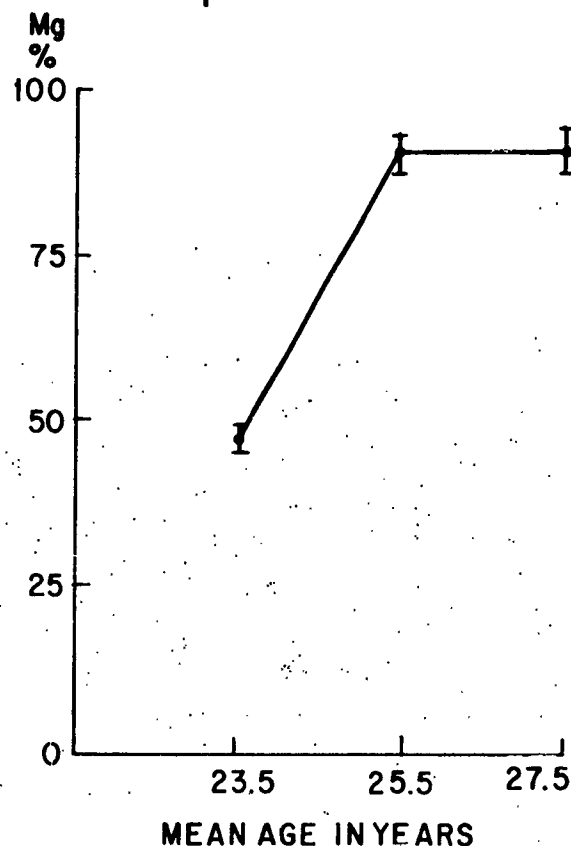


FIGURE 4

Mean concentration of serum lipoproteins, class S_f 20-400.

The mean serum phospholipid concentrations, shown in figure 2, have also followed an upward trend during the past six years. The pattern of change, however, is different from that seen in the cholesterol level. For example, between ages 23.5 and 25.5, the mean cholesterol concentration increased 14 mg./100 ml., while the mean phospholipid level did not change significantly. In the next two-year interval the mean cholesterol level decreased 13 mg./100 ml. but the mean phospholipid concentration appeared to increase, although not to a statistically significant extent.

One of the components of the low-density lipoproteins is the S_f 12-20 lipoprotein class.

Its concentration was measured at the start of the study and during the last three sampling years. Figure 3 shows that the only notable change recorded in this fraction was an increase between the ages of 23.5 and 25.5 years.

Another component of the low-density lipoproteins is the S_r 20-400 lipoprotein class, which was measured during only the last three sample years. The mean concentrations are plotted in figure 4. While the mean level rose significantly between ages 23.5 and 25.5, there was no further increase in this fraction through age 27.5 years.

The mean body weight of the subjects during the period of this study is plotted in figure 5. Between ages 19.6 and 21.5 there was a significant increase in body weight. It seems probable that this change represents a process of normal maturation, because no further change in the mean was recorded during the next two years. Between ages 23.5 and 25.5, however, there was a significant increase, which probably represents initial development of obesity. This interpretation is reasonable because the mean age of 23.5 years was reached in the calendar year 1956. It was during that year that the subjects were graduated from the U. S. Military Academy and were assigned to duty at various posts. This reassignment would involve a period of travel and change in routine that might well result in increased food consumption and decreased exercise, and thus cause the increases in mean values for body weight, serum cholesterol, and low-density lipoproteins recorded between ages 23.5 and 25.5. In any case, the fact that the mean weight remained unchanged during the subsequent two-year interval would suggest that the subjects had re-established an equality between caloric supply and demand.

The effect of diet upon serum lipoprotein levels has been investigated by many workers (see reviews by Lindgren and Nichols (5), Olson and Vester (6), and Albrink (7)). While the individual responses to changes in diet are highly variable, the lipoprotein fraction most affected by dietary changes is the low-density S_r 20-400 class. Usually smaller changes are

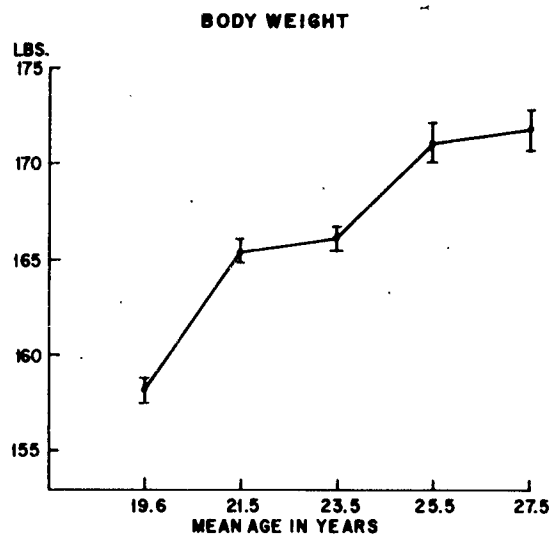


FIGURE 5
Mean body weight.

seen in the concentrations of S_r 12-20 and S_r 0-12 fractions. For example, Walker (8) observed that increased food consumption leading to gain in body weight produced marked elevation of the S_r 35-100 lipoproteins, with much smaller elevation of S_r 0-12.

In the light of such information, the data on the S_r 20-400 concentrations were examined closely for association with changes in body weight. In figure 6, the mean values for body weight and for S_r 20-400 lipoproteins are plotted for the years in which the S_r 20-400 class was measured. Note that there are two ordinate scales—one for weight, the other for lipoprotein. Obviously the changes in the means are in the same direction. However, the fact that two means change in the same direction does not necessarily imply that the two parameters change in the same direction in individual subjects. To ascertain whether changes in the S_r 20-400 lipoprotein fraction and in body weight are parallel in individual subjects, the direction of change in these parameters from the previous sample year was tabulated for each subject and is shown in table I. Subjects showing changes in the same direction in weight and in S_r 20-400 lipoprotein

concentration number 300 among a total of 431 in 1958 and 215 among a total of 363 in 1960. The proportion in 1960 is less than in 1958. This result is not unexpected, since the means

for body weight and S_r 20-400 lipoprotein concentration were unchanged between 1958 and 1960. In the absence of a trend, random variation in these values would lower the possibility of association to be observed between the variables.

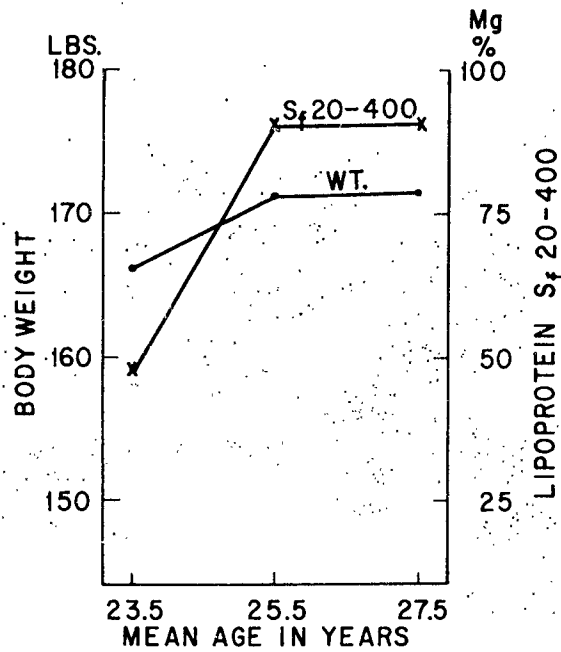


FIGURE 6

Comparison of mean values for S_r 20-400 lipoproteins with mean body weight.

The S_r 0-12 class is also a constituent of the low-density lipoproteins. This particular lipoprotein has been measured since the start of the study, and the mean concentrations are plotted in figure 7. The concentration of the S_r 0-12 fractions increased markedly between ages 21.5 and 25.5, but declined slightly during the last two-year interval.

Because the S_r 0-12 lipoprotein is rich in cholesterol, it is appropriate to compare the changes in concentration of cholesterol and of S_r 0-12 lipoprotein. Since cholesterol and cholesterol esters constitute approximately 50% of the weight of S_r 0-12 lipoprotein (9), a given change in the cholesterol concentration would require approximately twice as large a change in S_r 0-12 lipoprotein concentration if that class of lipoprotein were the only one present. Obviously, serum contains other lipoproteins in addition to the S_r 0-12 class, but to accentuate the relationship between the cholesterol and S_r 0-12 lipoprotein, the concentrations of these two substances were plotted in

TABLE I

Changes in weight versus changes in S_r 20-400 lipoprotein concentration during successive two-year intervals in individual subjects

Weight	23.5 to 25.5 years*			25.5 to 27.5 years*		
	S_r 20-400		Total	S_r 20-400		Total
	Increase	Decrease		Increase	Decrease	
Increase	259†	42	301	111	91	202
Decrease	89	41	130	57	104	161
Total	348	83	431	168	195	363
Percent change in same direction	69.6			59.2		

*Mean age at beginning and end of two-year interval.

†Number of subjects.

figure 8 using an ordinate scale for cholesterol that is one-half the scale for S_f 0-12 lipoprotein. On this plot, for a given change in cholesterol concentration, a change twice as great in lipoprotein concentration would cause the two curves to become parallel. It is apparent that there is overall similarity in both direction and magnitude of changes in this plot. The larger divergences in earlier years have been replaced by approximately parallel changes during the last two sampling years. These values, however, are mean values, and the same reservations apply here as were pointed out above in the body weight- S_f 20-400 lipoprotein relationships. Individual changes were, therefore, tabulated according to direction and analyzed. The results are recorded in table II. It is notable that the number of individuals showing changes in the same direction in concentration of cholesterol and of S_f 0-12 lipoproteins is higher in the last three sample years than in earlier years. Even in earlier years, however, there is a significant association between changes in cholesterol and in S_f 0-12 lipoprotein concentration.

The fact that the ratio of change in cholesterol concentration to change in S_f 0-12 lipoprotein concentration approaches 1:2 in the last two sampling years is undoubtedly the result of a change in the pattern of lipid transport that has occurred in these subjects. This shift is toward an increase in the concentration of S_f 0-12 lipoprotein and a decrease in that of the high-density lipoproteins. This pattern of change is evident in figure 9, which shows the mean concentrations of the total lipoproteins, the low-density, and the high-density fractions. The total lipoprotein concentration can be calculated for only the last three sample years because some fractions were not measured earlier. It is apparent that, while the mean total lipoprotein concentration has fluctuated, the value at age 27.5 years is close to the value at age 23.5. During that time, however, the mean concentration of the high-density lipoproteins has declined steadily. This decrease occurred first during a period when the mean concentrations of the low-density lipoproteins increased and later during a period when these concentrations remained unchanged or de-

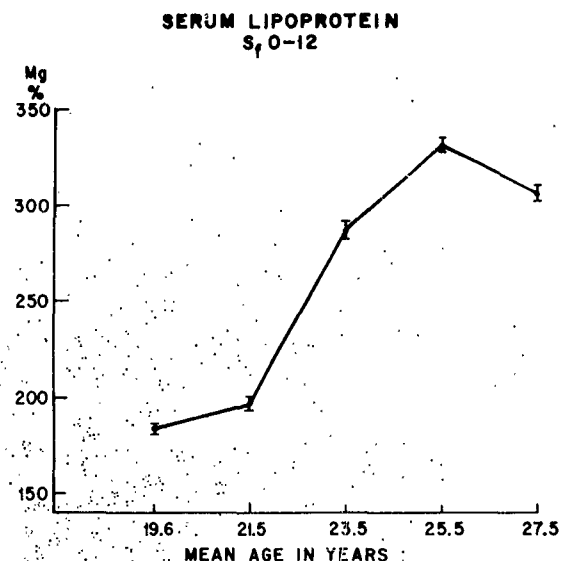


FIGURE 7
Mean concentration of serum lipoproteins, class S_f 0-12.

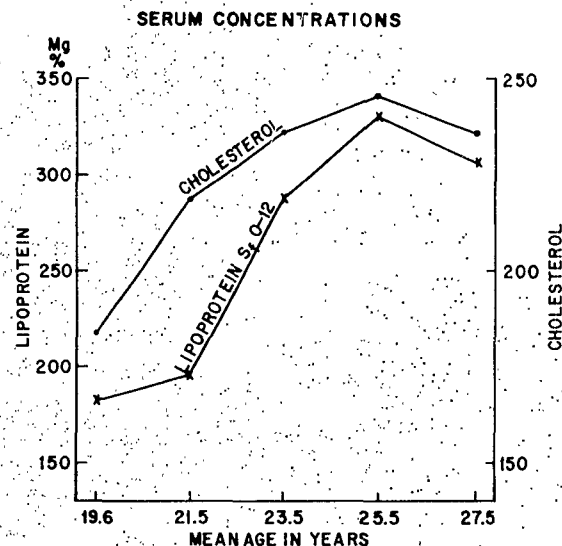


FIGURE 8
Comparison of mean concentrations of cholesterol and of S_f 0-12 lipoproteins.

creased. This fact indicates some degree of biologic independence between the high-density and low-density lipoprotein concentrations.

TABLE II

Changes in concentration of cholesterol and of S_r 0-12 lipoprotein during successive two-year intervals in individual subjects

S_r 0-12	19.6 to 21.5 years*			21.5 to 23.5 years*			23.5 to 25.5 years*			25.5 to 27.5 years*		
	Cholesterol		Total	Cholesterol		Total	Cholesterol		Total	Cholesterol		Total
	Increase	Decrease		Increase	Decrease		Increase	Decrease		Increase	Decrease	
Increase	204†	44	248	319	112	431	262	64	326	76	55	131
Decrease	125	29	154	13	10	23	45	76	121	52	213	265
Total	329	73	402	332	122	454	307	140	447	128	268	396
Percent change in same direction	58.0			72.5			75.6			73.0		

*Mean age at beginning and end of two-year interval.

†Number of subjects.

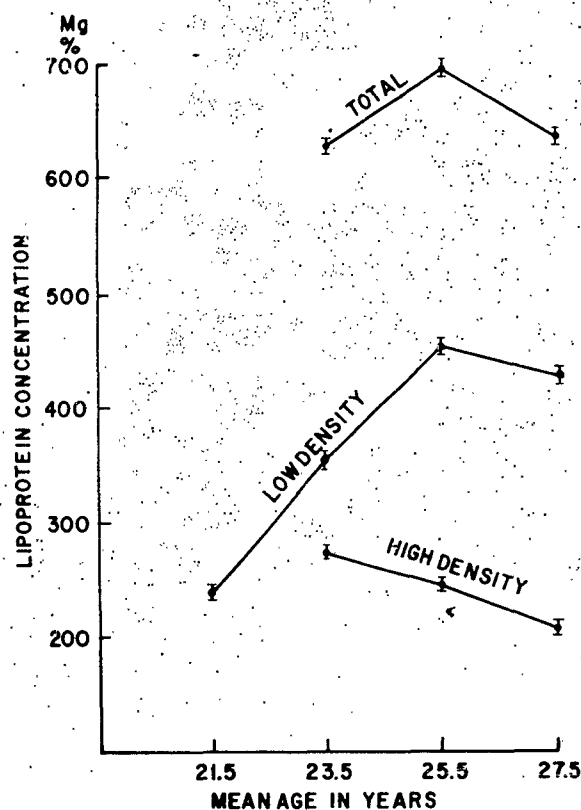


FIGURE 9

Mean concentrations of various serum lipids.

According to the early report of DeLalla et al. (10), one would expect small diminutions in the mean value for the high-density lipoprotein fraction between the ages of 18 and 40 in the male population, but the consistent decrease of concentration of this fraction with increasing age at this period of a man's life is surprising. This significant trend, however, is quite obvious in these subjects. The literature reports cited (5, 10) lead one to expect that the mean concentration of this fraction will not decrease much further and, in fact, will begin to rise somewhat in the near future.

The steady decline of the high-density lipoprotein fraction means that as these subjects have increased in age, an increasing proportion of the serum cholesterol has been transported by the low-density lipoproteins, principally by the S_r 0-12 fraction. Assuming that all serum cholesterol is transported in a lipoprotein complex (5), it is possible to estimate roughly the extent of this shift in cholesterol transport. Table III presents the pertinent data. As the subjects' mean age increased from 23.5 to 25.5 to 27.5 years, the mean serum high-density lipoprotein concentration successively decreased roughly 27 and 38 mg./100 ml., respectively. According to literature reports (9, 11, 12), the cholesterol-plus-cholesterol-esters content of

TABLE III
*Interrelationships of changes in concentrations of serum cholesterol
and lipoproteins*

Mean age (years)	Mean concentrations (mg./100 ml.)			Successive changes in mean concentrations (mg./100 ml.)				
	High-density lipoproteins	S _r 0-12	Cholesterol	Cholesterol	High-density lipoproteins	S _r 0-12 lipoprotein		
						Calculated*	Observed	Net
19.6		183.8	184.8					
21.5		195.8	219.3					
23.5	272.8	288.5	235.3					
25.5	245.5	331.6	249.1	+13.8	-27.3	+11	+43.1	+32
27.5	208.0	306.1	236.9	-12.2	-37.5	+15	-25.5	-41

*Calculated increase to replace decrease in high-density fraction. See text for method of calculation.

the high-density lipoproteins is approximately two-fifths that of the S_r 0-12 lipoproteins. Therefore, in terms of capacity to transport cholesterol, the decreases of 27 and 38 mg./100 ml. in high-density lipoproteins would require increases of 11 and 15 mg./100 ml., respectively, in S_r 0-12 lipoproteins to maintain an equal capacity to transport cholesterol. These computed values are recorded in column 7 of table III; the observed changes are given in column 8; and the difference between computed and observed changes is given in column 9. These values show that the increase in S_r 0-12 fraction at age 25.5 is in excess of what would be required to meet the deficit caused by the drop in high-density lipoprotein concentration. However, this excess, plus the S_r 20-400 lipoprotein, presumably is necessary to transport the increased cholesterol concentration that occurred at that time. At age 27.5 the S_r 0-12 concentration leaves a small deficit in net cholesterol-carrying capacity. This deficit is more than adequately filled by the serum concentration of S_r 12-400 lipoproteins. It is apparent, however, that at age 27.5 the distribution of cholesterol transport has changed so that less is carried by the high-density lipoproteins and more by the S_r 0-12 and S_r 12-400 lipoproteins than was carried at age 23.5.

The quantitative extent of this change in cholesterol transport may be estimated by using data taken from the literature on the composition of the lipoproteins (9, 11, 12). The composition of the S_r 0-12, S_r 12-400, and high-density lipoproteins is approximately 50, 20, and 20% cholesterol plus cholesterol esters, respectively. The distribution of cholesterol among the lipoprotein fractions, as calculated using these percentage compositions, is presented in table IV. If the figure of 50% is taken as a generous estimate (9) of the amount of cholesterol which could be transported by the S_r 0-12 lipoprotein fraction, the amount of cholesterol transported by that fraction would be no more than 50% of the serum concentration of that fraction. At age 19.6 years this amount would be no more than 92 mg. of cholesterol per 100 ml. of serum. The other components of the low-density lipoproteins (that is, the S_r 12-400 lipoproteins) were not measured at that time. They were measured two years later, however, when the mean concentration was only 43.5 mg./100 ml. This concentration of these lipoproteins presumably did not carry more than 10 mg. of cholesterol per 100 ml. of serum (9, 12). The mean concentration of the S_r 12-400 lipoproteins probably was no greater at age 19.6 than at age 21.5. If so, the amount of cholesterol transported by the S_r 0-12 and

TABLE IV
Calculated distribution of serum cholesterol among lipoproteins

Mean age (years)	Mean cholesterol concentration (mg./100 ml.)	Cholesterol distribution					
		In low-density lipoproteins				In high-density lipoproteins	
		50% \times S _r 0-12	20% \times S _r 12-400	Total	Relative fraction of total cholesterol	20% \times high density (mg./100 ml.)	Relative fraction of total cholesterol
		(mg./100 ml.)					
19.6	184.8	92	9	101	0.55		(0.45*)
21.5	219.3	98	9	107	0.49		(0.51)
23.5	235.3	144	14	158	0.67	55	0.23† (0.33)
25.5	249.1	166	24	190	0.76	49	0.20 (0.24)
27.5	236.9	153	24	177	0.75	42	0.18 (0.25)

*Calculated by subtracting value in column 6 from 1.00.

†Ratio of value in column 7 to mean cholesterol.

S_r 12-400 lipoproteins at age 19.6 totals not more than 102 mg. cholesterol per 100 ml. of serum, nor more than 55% of the total serum cholesterol at that age. Data on the concentration of high-density lipoproteins are not available for these subjects at age 19.6 years, but the cholesterol transported by that fraction would be the total cholesterol less that associated with the low-density fractions. Presumably, then, at least 45% of the serum cholesterol was carried by the high-density lipoproteins in this selected group of young men at age 19.6.

If percentage estimates as given above are applied to the data for age 27.5 years, the calculated maximal amount of cholesterol associated with the S_r 0-12 and S_r 12-400 lipoproteins is 153 and 24 mg. per 100 ml. of serum, respectively. Consequently the maximum total cholesterol associated with the low-density lipoproteins apparently is 177 mg. per 100 ml., or 75% of the total serum cholesterol. The remaining 25% of the serum cholesterol pre-

sumably was transported by the high-density lipoproteins.

It must be emphasized that the figures given above for cholesterol distribution are merely estimates. Several uncertainties enter into their computation. Outstanding among them are the use of mean concentration values for calculations and the assumption of constant lipid composition of the lipoprotein classes. We do not know whether the percentage composition of the lipoproteins varies from individual to individual or in the same individual over a period of time. Nevertheless, these estimates are probably accurate enough to emphasize the occurrence of a significant change in the pattern of cholesterol transport in these subjects during this period of time. The extent of this change is indicated by the fact that the proportion of total cholesterol associated with the high-density lipoproteins apparently has declined from approximately 45% at age 19.6 to approximately 25% at age 27.5 years. Meanwhile, the percent transported by the low-density fraction has risen from approximately

55% to approximately 75%. This is a significant shift in cholesterol transport.

These changes are reminiscent of the effects of administration of the androgenic hormones, such as testosterone. Russ and co-workers (13) and Furman and Howard (14), as well as others (15), have shown that testosterone administration produces an elevation of the beta (S_r 0-20) and a decrease of the alpha₁ (high-density) lipoprotein fractions. Administration of estrogens produces changes in the opposite direction. These effects of steroid hormones prompt consideration of the possibility that the changes observed in the lipid transport pattern of these subjects are caused by changes in the pattern of metabolism of androgens and estrogens associated with normal maturation.

The data of Hamburger (16) show that in men, 17-ketosteroid excretion rises from a low level in early boyhood to a maximum level near age 26, after which the amount excreted declines. Presumably, the 17-ketosteroids are primarily a reflection of androgen metabolism. Samuels (17) reported that, in man, the plasma concentration of dehydroepiandrosterone, which is one of the 17-ketosteroids, rises during puberty and reaches a maximum at age 25. Decreasing levels are found thereafter. On the other hand, the estrogen output in adult men remains relatively constant at all ages, according to the report of Pincus and co-workers (18). This fact, together with the changing pattern of androgen excretion with age in men, means that there would be an increasing androgen-to-estrogen ratio in the early twenties and a decreasing ratio during the late twenties and thereafter. Presumably, such a variation in androgen-to-estrogen ratios could produce an elevation of the S_r 0-20 and a decrease of the high-density lipoproteins during the early twenties, followed by a shift in the opposite direction. The data obtained thus far in this longitudinal study are in agreement with such a mechanism. Needless to say, such agreement does not in any way constitute proof of the possible hormonal mechanisms. Unfortunately,

no measurements of hormone excretion by the subjects in this study are available for evaluation of possible hormonal mechanisms.

It is a question of considerable importance whether these changes are, in fact, produced by alteration of hormonal metabolism associated with normal maturation. It is currently customary to attribute increases in serum lipids to factors such as diet, increased fat consumption, and lack of exercise. If the diet and lack of exercise mechanism is responsible, then a regimen of exercise and dietary control would be expected to reverse the unfavorable changes in the serum lipids. But if the hormonal mechanism is responsible, then exercise and diet control will be of limited value.

As pointed out above, the data on body weights and S_r 20-400 lipoprotein concentrations indicate that increased food intake and decreased exercise probably are partially responsible for the increases in serum lipid and lipoprotein concentrations. The decrease in concentration of high-density lipoproteins and the consequent shift in pattern of cholesterol transport, however, may possibly be the result of normal alterations in hormone metabolism associated with change in age. In other words, the possibility must be considered that the increases in serum cholesterol and phospholipid concentrations and the elevation of the ratio of low-density to high-density lipoproteins are the net effect of diet and caloric imbalance superimposed upon normal changes in hormone metabolism. Probably all these factors play some role in the lipid changes observed. It is obvious that further research must be conducted to ascertain what contribution is being made by each of these factors affecting lipid levels in the serum of these subjects. While the causes of the changes are being sought, the changes themselves must continue to be observed in the light of the original objective of the study—namely, to learn how well changes in serum lipids can predict susceptibility to, or proneness toward, subsequent occurrence of clinical symptoms of cardiovascular disease.

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